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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,580	03/29/2007	Shyam S. Mohapatra	USF.208TCXC1	6999

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,580	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22,24-26 and 32-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22,24-26 and 32-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 2/18/10.

Claims 1-11, 23, and 27-31 were cancelled and claims 32-43 were added.

Claims 12-22, 24-26, and 32-43 are under consideration in this Office Action.

All previous rejections are withdrawn in view of Applicant's amendments necessitating the following new grounds of rejection.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/481,738 and 60/522,180, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Neither of the cited priority documents provides support for the scope of nanoparticles

comprising a polynucleotide conjugated to chitosan. The '738 application does not disclose chitosan at all. The '180 application discloses nanoparticles comprising chitosan in the form of "NG042". This disclosure is does not provide support for the instantly recited compositions which do not limit the form of chitosan nanoparticle conjugate. NG042 has at least one characteristic that is not common to the genus of chitosan nanoparticle conjugates. For example, NG042 does not form a gel when reacted with 2-glycerol phosphate whereas another depolymerized chitosan (NG044) does. See e.g. US 20050266093 at paragraph 21. Accordingly, these two types of nanoparticles are considered to be structurally different, and the disclosure of only NG042 nanoparticles does not provide support for the broad genus of all of nanoparticles comprising a polynucleotide conjugated to chitosan. Accordingly the effective filing date of the instant claims is considered to be 12/6/2004.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-19, 22, 24, 26, and 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCray et al (US 7297786), Illum et al (US 6391318), Mohapatra (US 20030068333), and Manoharan et al (US 20050106598).

McCray taught methods of reducing the expression of respiratory syncytial virus genes comprising administering to airway epithelial cells a nucleic acid that is an siRNA or an expression plasmid encoding an shRNA, wherein the siRNAs or shRNAs target a nucleic acid sequence within an RSV gene or transcript. The nucleic acid can be delivered in a complex with a polymer such as chitosan. Delivery can be by intranasal route, aerosol delivery is contemplated, and discrete dosage forms are contemplated. See abstract; column 2, lines 22-51; column 4, lines 49-52; paragraph bridging columns 4 and 5; column 17, lines 7-14; paragraph bridging columns 19 and 20, especially column 20, lines 1-5; column 20, lines 51-54, and column 41, lines 32-34. The target gene can be the RSV NS1 gene (column 4, lines 50-52). The method can be employed therapeutically (after infection) or prophylactically (prior to infection). See e.g. column 41, lines 23-30. The method may be practiced in human or non-human mammals (see e.g. column 7, lines 3-16; column 41, lines 19-22; and references to the use of human cells throughout the disclosure).

McCray did not specifically teach a nanoparticulate complex of chitosan and siRNA.

Illum taught chitosan nanoparticle compositions for delivering plasmids to respiratory cells in vivo. The compositions were delivered as nasal drops or in the form of an aerosol system. See abstract, column 3, lines 12-24.

Mohapatra taught that chitosan nanoparticles allow increased bioavailability of DNA because of protection from degradation by serum nucleases in the matrix (paragraph 30).

Manoharan taught that chitosan could be used to form nanoparticulate complexes with oligonucleotides (paragraph 282). Oligonucleotides included DNA and RNA oligonucleotides (paragraph 50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the chitosan nanoparticles of Illum or Mohapatra for delivering the expression vectors of McCray because these nanoparticles were designed to deliver nucleic acids to the respiratory tract in vivo. It would have been similarly obvious to use these nanoparticles to deliver siRNAs in view of the suggestion of Manoharan to deliver RNA oligonucleotides using chitosan nanoparticles, and the suggestion of McCray to use chitosan complexes to deliver siRNAs.

The functional effects of reducing RSV titer, increasing production of type-I interferon, enhancing cellular immunity to RSV, inhibiting RSV-induced inflammation, and attenuating reinfection by RSV are considered to be inherent in a method of inhibiting expression of RSV NS1.

Thus the invention as a whole was prima facie obvious.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCray et al (US 7297786), Illum et al (US 6391318), Mohapatra (US 20030068333), and Manoharan et al (US 20050106598) as applied to claims 12-19, 22, 24, 26, and 32-43 above, and further in view of McSwiggen et al (US Patent 5,693,532) and Tuschl et al (US 20040259247)

The teachings of McCray, Illum, Mohapatra, and Manoharan are discussed above, and in combination render obvious methods of reducing the expression of RSV NS1 in a mammalian subject by intranasal administration siRNA, or shRNA expression vectors, wherein the siRNA or shRNA is directed against RSV NS1 RNA transcripts.

These references did not teach siRNA or shRNA directed against RSV NS2.

McSwiggen taught methods of inhibiting the replication of RSV in vivo through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. The ribozymes are targeted to NS1 and NS2 targets which reduce type-I interferon expression in cells. See columns 2-3, for example. Absent evidence to the contrary this would result in a relative increase in type I interferon expression. Preferred administration is by aerosol inhalation (see column 9, lines 8-16). The ribozymes can be expressed from vectors (column 5, lines 10-12 and 27-52.

Tuschl directly compared and contrasted ribozyme and RNAi technologies, stating at paragraph 148 that "…siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments."

It would have been obvious to one of ordinary skill in the art at the time of the invention to target both the NS1 and NS2 RSV genes for inhibition because McSwiggen suggested that this should be done. It would have been similarly obvious to use siRNA technology to do so because Tuschl taught that siRNAs provided greater silencing activity than ribozymes. It would have been obvious to use shRNA expression vectors

because shRNAs operate through the same RISC-mediated mechanism as siRNAs, thus one of skill would have had a reasonable expectation of success. Thus the invention as a whole was prima facie obvious.

Claims 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCray et al (US 7297786), Illum et al (US 6391318), Mohapatra (US 20030068333), and Manoharan et al (US 20050106598) as applied to claims 12-19, 22, 24, 26, and 32-43 above, and further in view of Prince et al (US 5,290,540) and Huang et al (US 6,586,579).

The teachings of McCray, Illum, Mohapatra, and Manoharan are discussed above, and in combination render obvious methods of reducing the expression of RSV NS1 in a mammalian subject by intranasal administration siRNA, or shRNA expression vectors, wherein the siRNA or shRNA is directed against RSV NS1 RNA transcripts.

These references did not teach a polynucleotide comprising a regulatory sequence that is a steroid response element.

Prince taught a method of treating RSV infection by aerosol topical application to the respiratory tract of an anti-viral agent and an anti-inflammatory steroid. See column 1, lines 26-38; paragraph bridging columns 6 and 7; column 7, lines 15-22; and claim 7.

In view of the suggestion of Prince to treat RSV infection by combining steroid treatment with administration of antivirals, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the antiviral treatment of McCray by

combining it with the use of a steroid applied to the lung. One would have been motivated to do so to obtain the advantages of each method.

These combined references do not teach the use of a steroid response element as an expression control sequence in the expression vector.

Huang taught that the use of inducible gene expression is advantageous, and that an exemplary inducible expression control element is a steroid response control element. See column 14, lines 13-16 and 22-25.

The selection of expression control sequences for an expression vector is considered to be a matter of design choice, such that the use of any expression control sequence that could function in the desired environment would be obvious absent evidence of secondary considerations. Further, in view of the teachings of Huang, one of ordinary skill in the art at the time of the invention clearly appreciated that inducible control of expression was beneficial, and that steroid responsive induction of gene expression was available. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a steroid inducible element to modulate expression of the ribozyme in the method of McCray as modified by Illum, Mohapatra, Manoharan, and Prince because the combined methods call for the use of steroids in the lung, and one of ordinary skill would clearly perceive that a steroid response element would allow the controllable induction of anti-viral shRNA expression, thereby advantageously allowing combination of the anti-inflammatory steroid effect with the antiviral shRNA effect.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 2/18/10 have been fully considered to the extent that they might apply to the new grounds of rejection above but they are not persuasive.

Applicant argues that the references previously relied on (McSwiggen, Tuschl, and Leaman) would not predictably generate success in delivering to airway cells a nanoparticle comprising a polynucleotide conjugated to chitosan, wherein the polynucleotide is an siRNA or expresses an shRNA such that expression of an RSV gene or transcript is reduced. This is unpersuasive in part because Leaman showed objectively that oligonucleotides could be delivered to cells in the lung to achieve expression inhibition through a hybridization-directed mechanism, and in part because those of skill recognized that the formation of nanoparticle complexes with polycations serves to stabilize oligonucleotides and polynucleotides against nucleolytic degradation. Accordingly, one of ordinary skill in the art aware of the prior art of record would have had a reasonable expectation of obtaining delivery of siRNAs and shRNA expression plasmids to airway epithelial cells using art recognized delivery compositions such as chitosan nanoparticles. Absent evidence to the contrary, such delivery results in inhibition of target RSV genes via the RNAi pathway, and results in the claimed functional effects. Applicant's statement that the results of Leaman cannot be predictably extrapolated to results with a nanoparticle comprising a polynucleotide conjugated to chitosan lacks any evidentiary or logical support, and is only a statement

of opinion. There is no reason of record that would indicate that the stabilizing 2'-O-methyl groups used by Leaman, and by Tuschl (paragraph 82), would not provide the same stabilizing effect in the siRNAs of McCray. Thus the prior art of record provides one of ordinary skill in the art a reasonable expectation of successfully delivering to airway epithelial cells functional siRNAs and shRNA expression vectors. The use of stabilizing nanoparticles only increases that expectation of success.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Fereydoun Sajjadi, can be reached at (571) 272-3311. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635